

**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Docket No: Q64848

Shinya WATANABE, et al.

Appln. No.: 09/875,158

Group Art Unit: 1616

Confirmation No.: 7273

Examiner: Barbara P. Badio

Filed: June 07, 2001

For: PRODUCTION PROCESS OF CYCLOHEXENYL METHYL KETONES

**RESPONSE TO NON-FINAL ACTION OF SEPTEMBER 26, 2003**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Please consider the following Applicants' response to the outstanding rejection of September 26, 2003, a three month Petition for Extension of Time and appropriate fee being filed herewith.

**RESPONSE**

The prior art considered: U.S. Patent 4,334,098 Mookherjee et al (Mookherjee); DE 3003894 Kampf (Kampf); U.S. Patent 3,914,242 Böhshagen et al (Boshagen).

The rejections:

Claims 1, 4, 5 and 15, all pending claims, are rejected under 35 U.S.C. § 103(a) over Mookherjee and Kampf and Boshagen.

The above rejections is respectfully traversed.

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The Examiner's position is set forth in the Action in detail and will not be repeated here except as appropriate to an understanding of Applicants' traversal which is now presented.

The Examiner's basic position appears to be that the only difference between the present invention and Mookherjee is in the final product obtained and the solvent used. Quoting the Examiner in the Action of September 26, 2003:

"As stated in the previous Office Action, Mookherjee teaches the same isomerization process as recited by the claimed invention. The difference is in the recitation of the solvent utilized."

...

"The lack of recitation of the identical end products as recited by instant claims is irrelevant because the skilled artisan would expect similar starting materials to result in similar end products and the court has held that the recitation of the products produced does not lend patentability to an old process."

Despite the Examiner's position that the only difference between the present invention and Mookherjee is in the final product(s) obtained and the solvent used, Applicants respectfully submit that a careful review of the present application and Mookherjee will establish that substantial differences exist regarding the:

final product(s) obtained;  
the catalyst used;  
the solvent used; and  
the reaction temperature used.

What the Examiner has done, it is respectfully submitted, is to focus on two factors (differences) between the present invention and Mookherjee and ignore other factors which reflect differences between the present invention and Mookherjee.

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In the Table below, the solvent, the catalyst, the reaction temperature, the reaction time and the product(s) obtained are compared between Mookherjee and the present invention.

Example	Solvent	Catalyst	Reaction Temperature	Reaction time	Product
1	EtOH	RhCl <sub>3</sub> ·3H <sub>2</sub> O	90°C	24hr	(1a'):(1b):(1c)= 10.5:88.3:1.2
2	H-(OCH <sub>2</sub> CH <sub>2</sub> ) <sub>4</sub> -OMe	t-BuOK	175°C	4hr	(1a'):(1b):(1c)= 12:61:27
3	DMSO	t-BuOK	100°C	4hr	(1a'):(1b):(1c)= 4:64:32
4	Toluene	PTSA	175°C	6hr	(1a'):(1b):(1c)= 17:56.5:26.5
5	DMSO	MeOK	120°C	2.5hr	(1a'):(1b):(1c)= 4.4:69.8:25.8
6	DMSO	MeONa	140-145°C	5hr	(1a'):(1b):(1c)= 28.9:49.2:21.9
7	DMSO	tBuOK	120°C	4hr	(1a'):(1b):(1c)= 52.3:32.9:14.8
8	DMSO	EtONa	130-140°C	6hr	(1a'):(1b):(1c)= 34.7:45.4:19.9
9	DMA	tBuOLi	140-145°C	6hr	(1a'):(1b):(1c)= 30.2:42.5:27.3
10	DMSO	KOH	170-190°C	6hr	(1a'):(1b):(1c)= 67.5:20.1:12.4
11	Cyclohexylamine	CyHxNHNa	125-135°C	3hr	(1a'):(1b):(1c)= 25.5:48.6:25.9
('098) Ex.II	EtOH	KOH	Refl. (80°C)	25hr	(1a'):(1b):(1c)= 100:0:0
('098) Ex.X	MeOH	MeONa	Refl. (70°C)	24hr	(1a'):(1b):(1c)= 100:0:0

In accordance with the present invention, a mixture of (1a'), (1b) and (1c) can be obtained as a final product. The reactions schemes in accordance with the present invention include (1) the use of an acidic catalyst (Examples 1 and 4) and (2) the use of a basic catalyst (Examples 2, 3 and 5-11).

In Example 1 of the present application, which uses an acidic catalyst, EtOH was used as the solvent (the same as Mookherjee). However, even if the reaction solvent in the case of using an acidic catalyst is the same as Mookherjee, this is not the sole condition determining what

product is obtained, rather, what product is obtained is also decided by the reaction temperature. The results in Example 4 support this point.

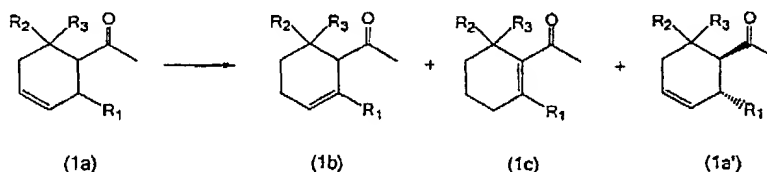
Thus, in the case of using an acidic catalyst in accordance with the present invention, the differences between the present invention and Mookherjee reside in the final product(s) obtained, the catalyst used and, additionally, a higher reaction temperature as compared to Mookherjee.

On the other hand, in the case of using a basic catalyst in accordance with the present invention, a mixture of (1a'), (1b) and (1c) is obtained due to the use of both the particular solvent and the particular reaction temperature. In the case of a basic solvent, an alcohol which limits the reaction temperature to up to about 80°C is not used as the solvent. Rather, in accordance with the present invention, a solvent which permits one to set the reaction temperature at 100°C or higher at normal pressure is used to obtain the desired final product(s).

Thus, in the case of using a basic catalyst, differences between the present invention and Mookherjee include the final product(s) obtained, the solvent used and the reaction temperature.

Applicants believe it appropriate to present a rather detailed analysis of the differences between the present invention, Mookherjee, Kampf and Boshagen.

The present invention relates to a process as shown in the following.



The present invention thus relates a process for producing 2-cyclohexenyl methyl ketone represented by general formula (1b), 1-cyclohexenyl methyl ketone represented by general

formula (1c), trans-3-cyclohexenyl methyl ketone represented by general formula (1a'), or a mixture thereof, by isomerizing 3-cyclohexenyl methyl ketone represented by general formula (1a) in the presence of an isomerization catalyst.

In Mookherjee the following process is disclosed.



Thus, in Mookherjee~~x~~ the process disclosed is a process for producing trans-3-cyclohexenyl methyl ketone by isomerizing cis-3-cyclohexenyl methyl ketone in an alcohol solvent in the presence of an alkali metal hydroxide or an alkali metal alkoxide. ✓

The Mookherjee reaction conditions (catalyst, solvent, reaction temperature) have earlier been commented on.

Kampf discloses a method relating to a process for isomerizing a double bond from a non-conjugated state in a 1,3-butadiene.

With respect to the isomerization conditions, the Kampf isomerization is carried out at 50 to 250°C using an alkali alcoholate as an isomerization catalyst and dimethyl sulfoxide, dimethylformamide, N-methylpyrrolidone, or the like, as a solvent.

In Boshagen, the following process is disclosed.



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formula (1c), trans-3-cyclohexenyl methyl ketone represented by general formula (1a'), or a mixture thereof, by isomerizing 3-cyclohexenyl methyl ketone represented by general formula (1a) in the presence of an isomerization catalyst.

In Mookherjee, the following process is disclosed.



Thus, in Mookherjee, the process disclosed is a process for producing trans-3-cyclohexenyl methyl ketone by isomerizing cis-3-cyclohexenyl methyl ketone in an alcohol solvent in the presence of an alkali metal hydroxide or an alkali metal alkoxide.

The Mookherjee reaction conditions (catalyst, solvent, reaction temperature) have earlier been commented on.

Kampf discloses a method relating to a process for isomerizing a double bond from a non-conjugated state in a 1,3-butadiene.

With respect to the isomerization conditions, the Kampf isomerization is carried out at 50 to 250°C using an alkali alcoholate as an isomerization catalyst and dimethyl sulfoxide, dimethylformamide, N-methylpyrrolidone, or the like, as a solvent.

In Boshagen, the following process is disclosed.



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Specifically (Example 1), the Boshagen process is a process for producing 2-ethyl-3-imino-1,2-benzisothiazoline hydrochloride by isomerizing 3-ethylamino-1,2-benzisothiazole hydrochloride in an aqueous solution at 50°C.

Although the Examiner has rejected the claims of the present application as obvious over the combination of Mookherjee and Kampf and Boshagen, Applicants respectfully submit that the combination of references does not reasonably suggest the present invention for the reasons now advanced.

In the Kampf process, a non-conjugated double bond is isomerized to a conjugated state. However, in the present invention, a main product of the isomerization of compound (1a) having an isolated double bond is compound (1b) in a non-conjugated state, although compound (1c) in a conjugated state is also obtained.

Namely, Applicants have tabulated the ratios of the resulting products in the present specification as follows.

Example 1: (1a):(1b):(1c) = 10.5:88.3:1.2  
Example 2: (1a):(1b):(1c) = 12:61:27  
Example 3: (1a):(1b):(1c) = 4:64:32  
Example 4: (1a):(1b):(1c) = 16:57:27  
Example 5: (1a):(1b):(1c) = 4.4:69.8:25.8  
Example 6: (1a):(1b):(1c) = 28.9:49.2:21.9  
Example 7: (1a):(1b):(1c) = 52.3:32.9:14.8  
Example 8: (1a):(1b):(1c) = 34.7:45.4:19.9  
Example 9: (1a):(1b):(1c) = 30.2:42.5:5.3  
Example 10: (1a):(1b):(1c) = 67.5:20.1:12.4  
Example 11: (1a):(1b):(1c) = 25.5:48.6:25.9

As is clear from the above, a main product among the products obtained in the isomerization of the double bond is compound (1b) in a non-conjugated state, not compound (1c)

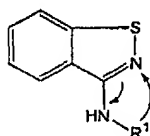
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in a non-conjugated state. The Kampf process is a process for obtaining a compound in a conjugated state, which relates to carbon-carbon double bonds. In the process of the invention, the "carbon-carbon double bond" is predicted upon the relation between a carbonyl group and a carbon-carbon double bond. Thus, the situation is quite different from that in Kampf. The present invention, of course, is not principally directed to achieving a compound which exhibits the conjugated state.

Thus, even if one of ordinary skill in the art were to combine Mookherjee with Kampf, for the reasons advanced the combination of Mookherjee and Kampf does not suggest the present invention.

The process of Boshagen relates to an isomerization reaction of an imine and further involves rearrangement of the  $R^1$  group of Boshagen. The reaction in Boshagen is a reaction which is specific to the imine compound and is only achieved in a compound where two nitrogen atoms are present in a 1,3-position relationship. Such a reaction is quite different from the isomerization of a carbon-carbon double bond. Further, because an aqueous solution is used, the solvent is also quite different.

The following formula schematically illustrates the teaching of Boshagen:



Thus, even assuming that one of ordinary skill in the art were to combine Mookherjee and Boshagen, Applicants respectfully submit that the present invention is not suggested by the combination of Mookherjee and Boshagen.



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As the Examiner no doubt suspects, it is Applicants' position that the combination of Mookherjee and Kampf and Boshagen does not suggest the present invention.

The following Table shows comparative experimental results which establish the differences of the present invention from Mookherjee.

Reference Mookherjee:

Example	Solvent	Catalyst	Reaction Temperature	Reaction time	Product
('098) Ex.II	EtOH	KOH	Refl. (80°C)	25hr	(1a):(1b):(1c)= 100:0:0
('098) Ex.X	MeOH	MeONa	Refl. (70°C)	24hr	(1a):(1b):(1c)= 100:0:0

Comparative Experiment (Only solvent was changed from Mookherjee):

Example	Solvent	Catalyst	Reaction Temperature	Reaction time	Product
Comparative Example 1	H-(OCH <sub>2</sub> CH <sub>2</sub> ) <sub>4</sub> -OMe	KOH	80°C	25hr	(1a):(1b):(1c)= 100:0:0
Comparative Example 2	H-(OCH <sub>2</sub> CH <sub>2</sub> ) <sub>4</sub> -OMe	MeONa	70°C	24hr	(1a):(1b):(1c)= 100:0:0
Comparative Example 3	DMSO	KOH	80°C	25hr	(1a):(1b):(1c)= 100:0:0
Comparative Example 4	DMSO	MeONa	70°C	24hr	(1a):(1b):(1c)= 100:0:0

Present invention:

Example	Solvent	Catalyst	Reaction Temperature	Reaction time	Product
Example 2	H-(OCH <sub>2</sub> CH <sub>2</sub> ) <sub>4</sub> -OMe	t-BuOK	175°C	4hr	(1a):(1b):(1c)= 12:61:27
Example 8	DMSO	EtONa	130-140°C	6hr	(1a):(1b):(1c)= 34.7:45.4:19.9

As is clear from the above, the  $\alpha$ -form (1b) and the  $\beta$ -form (1c) cannot be obtained by the process of Mookherjee. As is clear from the comparative experiments,  $\alpha$ -form (1b) and  $\beta$ -form (1c) cannot be obtained when the reaction temperature is 90°C or lower. Thus, the  $\alpha$ -form (1b)

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and the  $\beta$ -form (1c) can only be obtained when the conditions of the catalyst, the solvent, and the reaction temperature are all met.

The process of the present invention can provide the  $\alpha$ -form (1b) and the  $\beta$ -form (1c) which cannot be obtained by the process of Mookherjee and the processes of the comparative examples.

Simply stated, the reaction conditions (catalyst, solvent, reaction temperature) must be different from those of Mookherjee to obtain the products desired in accordance with the present invention.

As established above, the present invention is different from Mookherjee with respect to the final product and also the catalyst, solvent, and reaction temperature. As shown in the experiments above, the  $\alpha$ -form (1b) and the  $\beta$ -form (1c) according to the present invention are not obtained by the process of Mookherjee and there is no suggestion in Mookherjee to prepare the  $\alpha$ -form (1b) and the  $\beta$ -form (1c).

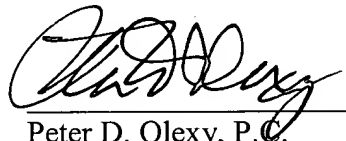
Although the Examiner's position seems to be to the effect that similar products would be obtained from similar starting materials, Applicants respectfully submit that the present invention is, considering all of the factors discussed above, not obvious over Mookherjee, because a different product is obtained by changing the reaction conditions, and this is the case even if Mookherjee were to be combined with Kampf and Boshagen.

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Withdrawal of all rejections is requested.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

  
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Date: March 26, 2004